# Efficacy and tolerability of pegylated interferon alpha 2b and ribavirin in chronic hepatitis C – a report from Eastern India

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***ABSTRACT***

*Aim:* To study the efficacy and tolerability of pegylated interferon alpha 2b and ribavirin therapy in a cohort of chronic hepatitis C patients.

*Methods:* In a prospective, open label, uncontrolled trial pegylated interferon alpha 2b (Viraferon Peg) 1.5 microgram/kg subcutaneously weekly plus daily ribavirin 800mg for 24 weeks in genotypes 2 & 3 and 1000mg for 48 weeks in genotypes 1 and 4 was administered to 16 patients of chronic hepatitis C. The primary end point was the sustained viral response. Therapy was prolonged by 3 months if the end of therapy response was not attained. Drug dosage was modified or temporarily discontinued if anaemia or bone marrow suppression developed.

*Results:* Both virological end of therapy response and sustained viral response were seen in 75% cases but not every patient who achieved end of therapy response had a sustained viral response. Relapse was seen in 31% cases and a pattern of delayed response was seen in 2 patients who later experienced a sustained viral response. Biochemical and virological responses were similar. A lower baseline viral load, genotype 3, a high ALT and the parenteral mode of viral acquisition were associated with higher sustained viral response rates. A good response was also seen in men, those over 50 years of age and those with normal baseline ALT. Most relapses occurred in genotype 3 patients whose age was less than 50 years; however the relapsing viral load was very low. 66% of previous interferon and ribavirin non-responders achieved sustained viral response. Treatment was well tolerated; temporary dose modification was required in 3 patients.

*Conclusion:* In Indian patients, a combination of peginterferon alpha 2b and ribavirin is safe and effective both as initial treatment of chronic hepatitis C and for use in previous non-responders.

*Keywords:* Peginterferon, ribavirin, hepatitis C

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## *INTRODUCTION*

A combination of pegylated interferon and ribavirin is currently the standard recommended therapy for chronic hepatitis C. It is given for 24 weeks for genotypes 2 and 3 and for 48 weeks for other genotypes. Western studies have yielded sustained viral response (SVR) rates of 40% to 50% for genotype 1 and 75% to 80% for genotypes 2 and 3. The outcome of therapy depends on host factors (age, sex, BMI, ethnicity, baseline ALT and stage of liver disease), viral factors (pretreatment viral load, genotype) and compliance with therapy.[1, 2] Data on this issue are scanty from India.[3] The aim of the present study was to evaluate the efficacy and tolerability of recombinant pegylated interferon (PEGIFN) alpha 2b and ribavirin in chronic hepatitis C patients and also to valuate the effects of the above factors on treatment outcome.

## *PATIENTS AND METHODS*

16 adult patients with chronic hepatitis C attending the liver clinic from June 2002 to June 2006 were included in a prospective, uncontrolled trial. An informed consent based on an appreciation and understanding of the study and its procedures was taken from each patient and the study was approved by the institutional ethics committee. Chronic hepatitis C was diagnosed based on Anti-HCV positivity (done by 3rd generation ELISA named QUALISA, Qualpro Diagnostics) for 6 months or more, quantitative serum HCV RNA determination (done by RT-PCR assay using Taqman probe, lower limit of detection 100 copies/ml) and genotyping (done by AB I 3100 Genetic Analyser, v3.1 cycle sequencing kit). Chronic liver disease was diagnosed based on biochemical, serological, ultrasonological, endoscopic and histological features as applicable. Liver biopsy was not binding for inclusion in to the study group. All patients belonged to Child Pugh class A. Other inclusion criteria comprised normal haemoglobin, total leukocyte count (TLC) and platelet count, creatinine, bilirubin, prothrombin time and thyroid function test and a negative test for HIV and any other cause of liver disease based on clinical suspicion and lab tests (HBsAg, ANF/ASMA, drug history, normal ceruloplasmin, ferritin, TIBC). All sexually active men and women were advised contraception for the treatment period and for 6 months thereafter. Consumption of alcohol was not allowed during the study.

Exclusion criteria compassed any degree of liver decompensation (Child Pugh class B or C including those with mild ascites and oesophageal varices grades 3 and 4), any severe systemic illness with or without autoimmunity, cancer, IV drug abuse, major psychiatric illness and thyroid disorder. Of the 35 patients diagnosed with chronic HCV related liver disease during this period, 16 met the above criteria.

Treatment schedule: Recombinant PEGIFN alpha 2b (Viraferon Peg, Fulford India) in a dose of 1.5 microgram/kg once a week subcutaneously and oral ribavirin (Rebetol, Fulford India) in a dose of 800mg/day for genotypes 2, 3 and 1000mg/day for genotypes 1, 4 in two divided doses were administered for 24 weeks to patients with genotypes 2, 3 and 48 weeks for genotypes 1, 4 infection. Therapy was prolonged where HCV RNA was detected at the end of therapy but where a partial

response was seen (greater than or equal to 2 log). Due to cost limitations, treatment was initially prolonged to 12 weeks and then up till 24 weeks if the HCV RNA was still positive. Therapy was discontinued whenever the HCV RNA became undetectable. A complete haemogram and testing for serum bilirubin, ALT and the prothrombin time were carried out at baseline, 2 weeks and 4 weeks, then monthly till the end of therapy and thereafter at 3 and 6 months post therapy. HCV RNA quantification was done at 12, 24, 36 (if necessary), 48 and 72 weeks (for genotype 1 cases and partial responders). Drug dosage was reduced (PEGIFN to 50 microgram and Ribavirin to 600mg) if the haemoglobin level fell below 9 g% and/or the TLC dropped below 3000/cumm and/or the platelet count fell below 75,000/cumm, and therapy was temporarily stopped if the corresponding values were less than 7g%, 2000 /cumm and 50,000/cumm respectively. Physical signs, side effects and drug compliance were monitored at each visit. The primary end point was SVR.

Therapeutic response was assessed as follows: (a) early viral response [EVR] was defined as either a negative score or at least a 2 log reduction in the HCV RNA levels from baseline to 12 weeks, (b) end of therapy response [ETR] was defined as negative RNA (virological response) and ALT normalisation (biochemical response) at the end of the treatment period, (c) comparable response when sustained for a 6–month period following completion of therapy was called a sustained viral response (SVR), (d) the patient was termed a non-responder if RNA amount was greater than or equal to the level at baseline, at 3 and 6 months of therapy and (e) a partial responder if the RNA was positive at the end of therapy but showed a higher level or equalled a 2 log decline from the baseline (i.e. partial ETR) or (f) a late complete responder if the RNA disappeared after 6 months of therapy; (g) relapse occurred if after achieving EOT response, SVR was not attained, (h) an interruption was defined as the initial disappearance of RNA that reappeared before the end of therapy. This was also regarded as a relapse. The Fischer exact test was used for statistical analysis and a p value less than 0.05 was taken as significant. The results were analyzed on an intension to treat basis.

## *RESULTS*

Baseline characteristics of the patients are shown in Table I. Most of the patients belonged to genotype 3 (12 of 16). None were overweight or obese. Liver biopsies were done in 3 patients; each biopsy demonstrated a histological activity index of more than 8 and stage 1 fibrosis. All patients completed therapy. ETR was 75% and the overall SVR was 75% but not all those who showed ETR had SVR. 12 of the 13 (92%) who showed an ETR also had an SVR. A phenomenon of delayed loss of HCV-RNA at 36 weeks was seen in 2 patients (late complete responders), less than 50 years of age, genotypes 2 and 3b with normal and increased ALT respectively. They were also partial responders. The patient with genotype 3b had an interrupted course (the only one of his kind in this series) but the HCV RNA level at 24 weeks was very low (partial responder) and subsequently disappeared at 36 weeks without further therapy. The patient with genotype 2 displayed a continuous decline in the HCV-RNA level till 24 weeks following which it disappeared at 36 weeks i.e. with 12 weeks of extra therapy. Both achieved an SVR on per protocol analysis. The ALT level normalised in all patients who had an elevated level before therapy but rose again in those who relapsed and remained normal in those who achieved an SVR. In all 4 patients with normal ALT at baseline, this remained so throughout the treatment course. 2 patients were non-responders, both aged more than 50 years. 1 had genotype 3a, normal ALT and high viral load ($>10^5$) at baseline and had relapsed following previous interferon alpha 2b and ribavirin therapy. The other had genotype 4 with increased ALT and low viral load (3517 copies/ml) at the start. He was in the habit of consuming alcohol but abstained during treatment. Relapse was seen in 4 cases, 3 had genotype 3 and 1 had genotype 1 infection, all except 1 were less than 50 years of age with viral load less than $10^5$. 2 of them (the ones with the least relapse viral load) showed spontaneous clearance after 3 and 6 months. 1 relapsed at year 1 after achieving an SVR. The results are summarised in Table II.

Table I: Baseline characteristics of patients

| | |
|---|---|
| 1. | Age (mean + S.D): 47.75 + 11.83 years [Range 22–65] |
| 2. | Sex: M:F=12:4 |
| 3. | Body weight [mean+S.D]:56+3.8KG[Range 48–64] |
| 4. | BMI [mean+S.D]:20.3+1.2[Range 18.2–22.4] |
| 5. | Mean follow up:30months |
| 6. | Mode of infection: |
| | [a] Unknown source:10 |
| | [b] Health care worker:1 |
| | [c] Blood transfusion (thalassemia):3 |
| | [d] Voluntary blood donor:2 |
| 7. | Genotypes: |
| | [a] 1a:1 |
| | [b] 1b:1 |
| | [c] 2:1 |
| | [d] 3a:6 |
| | [e] 3b:6 |
| | [f] 4:1 |
| 8. | Anti HCV positivity : All 16 |
| 9. | Median HCV-RNA load: 70,278 copies/ml [Range 3517–40 X 106] |
| 10. | Mean ALT: 56+16 IU/L [Range 17–120] (normal upto 40) |
| 11. | Mean hemoglobin:11.8+1.6gm/dl[Range 10.2–14] |
| 12. | Total leucocyte count: 7200+1360/cu.mm[Range 4600–9400] |
| 13. | Platelet count: 1.84+0.31 lac/cu.mm [Range 1.7–2.2] |
| 14. | Spouses of all patients negative for Anti HCV |
| 15. | Significant alcohol intake: 2 |
| 16. | Pretreatment diabetic :2 |
| 17. | Previous therapy with Interferon alpha [3MU alternate day] and Ribavirin [800mg/day] for 6 months |

Table II: Viral response rates during and after therapy in relation to different factors

| Item | N | 12 wks | 24wks | 36wks | 48wks | 72wks | Overall SVR |
|---|---|---|---|---|---|---|---|
| Total | 16 | 13[81%] | 12[75%] | 2 | 12[75%] | 4/6 | 12[75%] |
| **Age** | | | | | | | |
| <50yr | 8 | 7[75%] | 6[75%] | 2 | 7[87%] | 2/3 | 6[75%] |
| >or=50yr | 8 | 6[75%] | 6[75%] | – | 5[62%] | 1/1 | 6[75%] |
| **Sex** | | | | | | | |
| M | 12 | 9[75%] | 9[75%] | 1 | 9[75%] | 3/5 | 9[75%] |
| F | 4 | 4[100%] | 3[75%] | 1 | 4[100%] | 1/2 | 3[75%] |
| **Viral load [copies/ml]** | | | | | | | |
| $<10^6$ | 13 | 11[85%] | 10[77%] | 2 | 11[85%] | 4/6 | 11[85%] |
| $>=10^6$ | 3 | 2[67%] | 2[67%] | – | 1[33%] | 0 | 1[33%] |
| **ALT** | | | | | | | |
| Normal | 4 | 2[50%] | 2[50%] | 1 | 3[75%] | 1/2 | 3[75%] |
| >Normal | 12 | 11[92%] | 10[83%] | 1 | 9[75%] | 1/3 | 10[83%] |
| **Mode of Infection** | | | | | | | |
| Via blood | 6 | 6[100%] | 5[83%] | 1 | 6[100%] | 1/2 | 5[83%] |
| Unknown | 10 | 7[70%] | 7[70%] | 1 | 6[100%] | 3/4 | 7[70%] |
| **Genotype** | | | | | | | |
| 1 | 2 | 2 | 2 | – | 2 | 1 | 1[50%] |
| 2 | 1 | 0 | 0 | 1 | 1 | 1 | 1[100%] |
| 3 | 12 | 11[92%] | 10[83%] | 1 | 9[75%] | 2/3 | 10[83%] |
| 4 | 1 | 0 | 0 | – | 0 | – | 0 |
| Pretreated with ribavirin & interferon alpha | 3 | 2 | 2 | – | 2 | – | 2[66%] |

*Each subgroup within groups 1 to 5 contains 1 patient of genotype1. None of the subgroup differences are statistically significant.*

*Factors determining the outcome of therapy:* Though none of the differences in subgroup responses was statistically significant, those with higher ALT level, low viral load, genotypes 2 and 3 and the parenterally infected showed a tendency to higher SVR rates. Age and sex did not affect the SVR rates except that both non-responders were men more than 50 years of age. Of the 2 diabetics 1 attained an SVR. 66% of those who had previously relapsed with interferon alpha 2b and ribavirin treatment achieved SVR, all belonged to genotype 3a.

*Side effects :* All patients suffered a flu-like febrile reaction of variable intensity in the first few weeks of therapy which was easily controlled with 1–2 tablets of paracetamol taken before the PEGIFN injection and which subsequently resolved. 3 (19%) experienced a significant fall in haemoglobin level and 1 developed pancytopenia which mandated stopping of therapy for 2 weeks following which they improved. The other 2 had thalassaemia, required blood transfusion (2 units each) and a temporary reduction in ribavirin dosage to 600 mg/day for 2 weeks. Another 3 patients had non-significant fall in the levels of haemoglobin total leukocytes and platelets which did not require dose alteration. 1 had an exacerbation of pre-existing rheumatoid arthritis and both diabetics had their disease well controlled with insulin injection during the treatment period. Significant mood swings, infections, thyroid disorders and local or systemic reactions were not observed in any patient.

## *DISCUSSION*

This prospective trial imparts early data on the safety and efficacy of PEGIFN alpha 2b and ribavirin in the treatment of chronic hepatitis C. The overall genotype related response rate was comparable to that obtained from Western data[1] but was higher than that reported from the rest of India[3] as this series included patients of cirrhosis who showed lower response rates. The predominant genotype was 3 as has been previously reported from India.[3–5] Virological and biochemical responses went hand in hand. The relapse rate (31%) was slightly high,[1] in particular 4 of 5 (80%) relapses occurred with genotype 3; this has also been reported from the rest of India.[3] In a majority of cases (80%), the viral load in the relapsed patient was very low (in hundreds of copies/ml) and 3 cases showed spontaneous clearance of the virus without further therapy. Of special note was the fact that 2 patients had a delayed response at 36 weeks but both had an SVR. Therefore, for genotype 3 infection in developing countries, if the viral load is very low at the end of therapy a policy of wait and watch for 3 to 6 months may be adopted in the anticipation of spontaneous viral clearance, therapy may even be prolonged for 12 weeks if drug affordability is not a problem. The factors determining therapy outcome were similar to those seen in the West[1, 2] and in the rest of India.[3] Normal ALT should not preclude therapy, particularly if the patient opts for it, as a proportion of these patients may go on to develop significant liver disease.[6,7] Recent studies have shown that the response rate is independent of the ALT level.[8] Advanced age may be regarded as associated with increased liver fibrosis and thus decreased response rates but here too therapy should not be withheld as recent studies have shown a good response rate[9] as also seen in our study. Male patients also demonstrated good response rates in our trial. A particularly interesting observation was a slightly better SVR among patients who acquired infection via the parenteral route. It is possible that these patients undergo testing for HCV more frequently; the disease may thus be detected at an early stage when treatment responses are better; those who have an unknown mode of infection may remain undiagnosed till a later stage. In our study 5 out of 6 patients were less than 50 years old and were female in whom treatment response is generally better. SVR was 50% among the alcohol drinkers although both patients abstained during the trial. Alcohol may increase fibrosis, thus reducing the response.[10] Since none of our patients was overweight, this effect on therapy could not be studied. An encouraging fact was the 66% response rate seen in patients who had previously relapsed with plain interferon and ribavirin therapy (all of genotype 3a), and this was much higher than that reported from the West.[2,10] All spouses of patients were Anti-HCV negative indicating low sexual or intra-familial transmission. We concluded that liver biopsy is not essential during treatment since it is invasive, potentially harmful and may result in sampling error; it should thus be avoided if the patient opts for

therapy without it, particularly for patients with genotypes 2, 3 infection in whom the response rate is high. Since most of our patients had genotypes 2 and 3 infection that did not warrant liver biopsy, it was deferred in most cases.

Therapy was generally well tolerated except for the development of reversible dose dependent bone marrow suppression and ribavirin-induced anaemia in 19% cases. None required discontinuation of therapy. This was analogous to the Indian data[3] but lower than that seen in the West.[10] The main drawback of our study was its uncontrolled nature and the small patient number (which reduces the import of significance tests), but this was expected due to the formidable cost of therapy in our country. Nevertheless, this study affords early prospective data on the efficacy, safety and factors determining outcome of therapy.

In conclusion, the efficacy and tolerability of combination of PEGIFN alpha 2b and Ribavirin therapy in patients of chronic hepatitis C in India is encouraging and more or less similar to that seen in the West. The relapse rate was mildly high, particularly in patients of genotype 3 infection. A pattern of delayed response to therapy was seen. The response rate was also favourable in the patients and those more than 50 years of age. High SVR was demonstrated among those who had previously relapsed. Future controlled studies are needed for verification.

## *REFERENCES*


1. Hoofnagle JH, Seeff LB. Peginterferon and Ribavirin for chronic hepatitis C. N Engl J Med. 2006;355:2444–51.
2. Strader DB, Wright T, Thomas DL, Seeff LB**,** American Association for the Study of Liver Diseases. Diagnosis, management and treatment of Hepatitis C. Hepatology. 2004;39:1147–71.
3. Sood A, Midha V, Sood N, Bansal M. Pegylated Interferon alpha 2b and oral ribavirin in patients with HCV-related cirrhosis. Ind J Gastroenterol. 2006;25:283-5.
4. Hazari S, Pande SK, Gupta SD, Batra Y, Singh R, Acharya SK. Treatment of Hepatitis C virus infection in patients of northern India. J Gastroenterol Hepatol. 2004;19:1058-65.
5. Chowdhury A, Santra A, Chaudhuri S, Dhali GK, Choudhuri S, Maity SG, et al. Hepatitis C virus infection in the general population : a community-based study in West Bengal, India. Hepatology. 2003;37:802–9.
6. Dor-Mohammadi T, Daryani NE, Bashashati M, Hashtrudi A, Haghpaneh B, Sayyan A, et al. Relationship between serum ALT levels and liver histology in chronic hepatitis C-infected patients. Ind J Gastroentol. 2005;24:49–51.
7. Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminases. J Hepatol. 2003;38:511–7.
8. Hui CK, Monto A, Belaye T, Lau E, Wright TL. Outcomes of interferon alpha and ribavirin treatment for chronic hepatitis C in patients with normal serum aminotransferases. Gut. 2003;52:1644–8.
9. Thabut D, Le Calvez S, Thibault V, Massard J, Munteanu M, DiMartino V et al. Hepatitis C in 6865 patients 65 years or older: a severe and neglected curable disease?. Am J Gastroenterol. 2006;101:1260–7.